

Applicants : Alexander Gad and Dora Lis
Serial No. : 10/792,311
Filed : March 2, 2004
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In the Claims

Please amend the claims by replacing all prior versions, and listings, of claims pursuant to 37 C.F.R. §1.121(c) as follows:

1-122. (Canceled)

123. (Currently Amended) In a process for obtaining a pharmaceutical product containing a mixture of polypeptides, each of which consists essentially of alanine, glutamic acid, tyrosine and lysine, wherein the mixture has an average molecular weight from 4000 to 13,000 Daltons and in the mixture the molar fraction of alanine is 0.427, of glutamic acid is 0.141, of lysine is 0.337 and of tyrosine is 0.093 and wherein during the process includes determining the molecular weight distribution of a batch of a-an aqueous mixture of polypeptides, each of which consists essentially of alanine, glutamic acid, tyrosine and lysine, is tested using a gel permeation chromatography column to determine whether the mixture has an average molecular weight from 4000 to 13,000 Daltons for inclusion in the pharmaceutical product, the improvement comprising

calibrating the molecular weight obtained using the gel permeation chromatography column by subjecting a plurality of molecular weight markers, each of which is a polypeptide consisting essentially of alanine, glutamic acid, tyrosine and lysine and having a predetermined amino acid sequence, to chromatography on the column to establish a relationship between retention time on the column and molecular weight.

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124-126. (Canceled)

127. (Previously presented) The process of claim 123, wherein the gel permeation chromatography column comprises a cross-linked agarose-based medium, with an exclusion limit of 2×10^6 Daltons, an optimal separation range of 1000 to 3×10^5 Daltons, and a bead diameter of 20-40 μm .

128. (Previously presented) The process of claim 127, wherein the gel permeation chromatography column is Superose 12.

129. (Previously amended) The process of claim 123, wherein in the molecular weight markers the molar fraction of alanine is 0.38 to 0.5, of glutamic acid is 0.13 to 0.15, of tyrosine is 0.08 to 0.10 and of lysine is 0.3 to 0.4.

130. (Previously Amended) The process of claim 129, wherein in the molecular weight markers the molar fraction of alanine is 0.422 to 0.444, of glutamic acid is 0.133 to 0.143, of tyrosine is 0.086 to 0.093 and of lysine is 0.333 to 0.349.

131. (Previously presented) The process of claim 123, wherein one of the molecular weight markers is selected from the group consisting of

AKKYAKKEKAACKKAYKKEAKAKAAEAAKEAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAYEKAAAEKAAKEAAYEA (SEQ ID NO:2);

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AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAEAKYKAEAAKAAKEAAYE
A (SEQ ID NO:3);
AKKYAKKEKAYAKAKKA EAKA AAKKAKAEAKKYAKAAKAEKKEYAAAAEAKYKAEAA
KAAAKEAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKRAYKAEAAKAAAKEAAYEA (SEQ ID NO:6); and
AKKYAKKA EKAYAKKAKAA EKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKAAKAEKKEYAAAAEAKKAEAAKAYKAEAAKAAAKEAAYEA
(SEQ ID NO:7).

wherein A represents alanine, K represents lysine, Y
represents tyrosine, and E represents glutamic acid.

132. (Previously presented) The process of claim 123,
wherein the plurality of molecular weight markers is

AKKYAKKEKA AKKAYKKEAKAKAAEAAAKEAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKA AKYEKAAAEKAAAKEAAYEA (SEQ ID
NO:2);
AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAYE
A (SEQ ID NO:3);
AKKYAKKEKAYAKAKKA EAKA AAKKAKAEAKKYAKAAKAEKKEYAAAAEAKYKAEAA
KAAAKEAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKA EKA AAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAYKAEAAKAAAKEAAYEA (SEQ ID NO:6); and
AKKYAKKA EKAYAKKAKAA EKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKAAKAEKKEYAAAAEAKKAEAAKAYKAEAAKAAAKEAAYEA
(SEQ ID NO:7).

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wherein A represents alanine, K represents lysine, Y represents tyrosine, and E represents glutamic acid.

133. (Previously Amended) The process of claim 123, wherein the pharmaceutical product is lyophilized.

134. (Previously Amended) A process for obtaining a pharmaceutical product containing a mixture of polypeptides, each of which consists essentially of alanine, glutamic acid, tyrosine and lysine, wherein the mixture has an average molecular weight from 4000 to 13,000 Daltons and in the mixture the molar fraction of alanine is 0.427, of glutamic acid is 0.141, of lysine is 0.337 and of tyrosine is 0.093, which comprises obtaining a batch of a mixture of polypeptides, each of which consists essentially of alanine, glutamic acid, tyrosine and lysine;

determining the average molecular weight of the mixture of polypeptides in the batch using a molecular weight-calibrated gel permeation chromatography column; and

including in the pharmaceutical product the mixture if the mixture is determined to have an average molecular weight from 4000 to 13,000 Daltons,

wherein the gel permeation chromatography column is calibrated by subjecting a plurality of molecular weight markers to chromatography on the column to establish a relationship between the retention time on the column and molecular weight, wherein each of the markers is a polypeptide consisting essentially of

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alanine, glutamic acid, tyrosine and lysine and has a predetermined amino sequence.

135-137. (Canceled)

138. (Previously presented) The process of claim 134, wherein the gel permeation chromatography column comprises a cross-linked agarose-based medium, with an exclusion limit of 2×10^6 Daltons, an optimal separation range of 1000 to 3×10^5 Daltons, and a bead diameter of 20-40 μm .

139. (Previously presented) The process of claim 138, wherein the gel permeation chromatography column is Superose 12.

140. (Previously Amended) The process of claim 134, wherein in the molecular weight markers the molar fraction of alanine is 0.38 to 0.5, of glutamic acid is 0.13 to 0.15, of tyrosine is 0.08 to 0.10 and of lysine is 0.3 to 0.4.

141. (Previously Amended) The process of claim 140, wherein in the molecular weight markers the molar fraction of alanine is 0.422 to 0.444, of glutamic acid is 0.133 to 0.143, of tyrosine is 0.086 to 0.093 and of lysine is 0.333 to 0.349.

142. (Previously presented) The process of claim 134, wherein one of the molecular weight markers is selected from the group consisting of

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AKKYAKKEKAACKKAYKKEAKAKAAEAAAKEAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAYEKAAAEEKAAAKEAAYEA (SEQ ID
NO:2);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAYE
A (SEQ ID NO:3);
AKKYAKKEKAYAKAKKAKEAKAAKKAKAEAKKYAKAAKAEKKEYAAAAEAKYKAEAA
KAAAKEAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAYKAEAAKAAAKEAAYEA (SEQ ID NO:6); and
AKKYAKKAEEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKAAKAEKKEYAAAAEAKKAEAAKAYKAEAAKAAAKEAAYEA
(SEQ ID NO:7).

wherein A represents alanine, K represents lysine, Y
represents tyrosine, and E represents glutamic acid.

143. (Previously presented) The process of claim 134,
wherein the plurality of molecular weight markers is

AKKYAKKEKAACKKAYKKEAKAKAAEAAAKEAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAYEKAAAEEKAAAKEAAYEA (SEQ ID
NO:2);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAYE
A (SEQ ID NO:3);
AKKYAKKEKAYAKAKKAKEAKAAKKAKAEAKKYAKAAKAEKKEYAAAAEAKYKAEAA
KAAAKEAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKAKEKAACKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAYKAEAAKAAAKEAAYEA (SEQ ID NO:6); and

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AKKYAKKAEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKAAKAEKKEYAAAEAKKAEAAKAYKAEAAKAAAKEAAAYEA
(SEQ ID NO:7),

wherein A represents alanine, K represents lysine, Y
represents tyrosine, and E represents glutamic acid.

144. (Currently Amended) The process of claim 134, further
comprising a step of lyophilizing the mixture ~~having~~
~~the average molecular weight from 4,000 to 13,000~~
~~Daltons~~ of polypeptides.

145. (Previously Amended) A process for determining the
average molecular weight of an aqueous mixture of
polypeptides, each of which consists essentially of
alanine, glutamic acid, tyrosine and lysine, wherein in
the mixture the molar fraction of alanine is 0.427, of
glutamic acid is 0.141, of lysine is 0.337 and of
tyrosine is 0.093, which comprises subjecting the
mixture to chromatography on a molecular weight-
calibrated gel permeation chromatography column so as
to determine the average molecular weight of the
mixture, wherein the gel permeation chromatography
column is calibrated by subjecting a plurality of
molecular weight markers to chromatography on the
column to establish a relationship between retention
time on the column and molecular weight, wherein each
of the markers is a polypeptide consisting essentially
of alanine, glutamic acid, tyrosine and lysine and has
a predetermined amino acid sequence.

146-148. (Canceled)

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149. (Previously presented) The process of claim 145, wherein the gel permeation chromatography column comprises a cross-linked agarose-based medium, with an exclusion limit of 2×10^6 Daltons, an optimal separation range of 1000 to 3×10^5 Daltons, and a bead diameter of 20-40 μm .
150. (Previously presented) The process of claim 149, wherein the gel permeation chromatography column is Superose 12.
151. (Previously Amended) The process of claim 145, wherein in the molecular weight markers the molar fraction of alanine is 0.38 to 0.5, of glutamic acid is 0.13 to 0.15, of tyrosine is 0.08 to 0.10 and of lysine is 0.3 to 0.4.
152. (Previously Amended) The process of claim 151, wherein in the molecular weight markers the molar fraction of alanine is 0.422 to 0.444, of glutamic acid is 0.133 to 0.143, of tyrosine is 0.086 to 0.093 and of lysine is 0.333 to 0.349.
153. (Previously presented) The process of claim 145, wherein one of the molecular weight markers is selected from the group consisting of
- AKKYAKKEKAACKKAYKKEAKAKAAEAAAKEAAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAKYEKAAAEKAAAKEAAAYEA (SEQ ID NO:2);

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AKKYAKKEKAYAKKAEKAAKKAEEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAYE
A (SEQ ID NO:3);
AKKYAKKEKAYAKAKKAEAKAAKKAKAEAKKYAKAAKAEKKEYAAAEEAKYKAEAA
KAAAKEAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKAEKAAKKAEEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKAEKAAKKAEEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKKAYKAEAAKAAAKEAAYEA (SEQ ID NO:6); and
AKKYAKKAEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKAAKAEKKEYAAAEEAKKAEAAKAYKAEAAKAAAKEAAYEA
(SEQ ID NO:7),

wherein A represents alanine, K represents lysine, Y
represents tyrosine, and E represents glutamic acid.

154. (Previously presented) The process of claim 145,
wherein the plurality of molecular weight markers is

AKKYAKKEKAAKKAYKKEAKAKAAEAAAKEAAYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAKYEKAAAEKAAAKEAAYEA (SEQ ID
NO:2);
AKKYAKKEKAYAKKAEKAAKKAEEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAYE
A (SEQ ID NO:3);
AKKYAKKEKAYAKAKKAEAKAAKKAKAEAKKYAKAAKAEKKEYAAAEEAKYKAEAA
KAAAKEAAYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKAEKAAKKAEEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKAEKAAKKAEEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKKAYKAEAAKAAAKEAAYEA (SEQ ID NO:6); and
AKKYAKKAEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKAAKAEKKEYAAAEEAKKAEAAKAYKAEAAKAAAKEAAYEA
(SEQ ID NO:7),

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wherein A represents alanine, K represents lysine, Y represents tyrosine, and E represents glutamic acid.

155. (Previously Amended) A process for determining whether an aqueous mixture of polypeptides, each of which consists essentially of alanine, glutamic acid, tyrosine and lysine, has an average molecular weight from 4000 to 13,000 Daltons, wherein in the mixture the molar fraction of alanine is 0.427, of glutamic acid is 0.141, of lysine is 0.337 and of tyrosine is 0.093, which process comprises subjecting the mixture to a calibrated gel permeation chromatography column to determine the average molecular weight of the mixture wherein the gel permeation chromatography column is calibrated by subjecting a plurality of molecular weight markers to chromatography on the column to establish a relationship between retention time on the column and molecular weight, wherein each of the markers is a polypeptide consisting essentially of alanine, glutamic acid, tyrosine and lysine and has a predetermined amino acid sequence.

156-158. (Canceled)

159. (Previously presented) The process of claim 155, wherein the gel permeation chromatography column comprises a cross-linked agarose-based medium, with an exclusion limit of 2×10^6 Daltons, an optimal separation range of 1000 to 3×10^5 Daltons, and a bead diameter of 20-40 μm .

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160. (Previously presented) The process of claim 159, wherein the gel permeation chromatography column is Superose 12.
161. (Previously amended) The process of claim 155, wherein in the molecular weight markers the molar fraction of alanine is 0.38 to 0.5, of glutamic acid is 0.13 to 0.15, of tyrosine is 0.08 to 0.10 and of lysine is 0.3 to 0.4.
162. (Previously amended) The process of claim 161, wherein in the molecular weight markers the molar fraction of alanine is 0.422 to 0.444, of glutamic acid is 0.133 to 0.143, of tyrosine is 0.086 to 0.093 and of lysine is 0.333 to 0.349.
163. (Previously presented) The process of claim 155, wherein one of the molecular weight markers is selected from the group consisting of
- AKKYAKKEKAACKKAYKKEAKAKAAEAAAKEAAYEA (SEQ ID NO:1);
- AKKYAKKAKAEKAKKAYKAAEAKKAAKYEKAAAEKAAAKEAAYEA (SEQ ID NO:2);
- AKKYAKKEKAYAKKAKEAKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:3);
- AKKYAKKEKAYAKKAEAKKAEAKKAKAEAKKYAKAAKAEKKEYAAAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:4);
- AKKYAKKEKAYAKKAKEAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA AAEAKYKAEAAKAAAKEAAYEA (SEQ ID NO:5);
- AKKYAKKEKAYAKKAKEAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA AAEAKYKAEAAKAYKAEAAKAAAKEAAYEA (SEQ ID NO:6); and

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AKKYAKKAEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKAAKAEKKEYAAAEAKKAEAAKAYKAEAAKAAAKEAAEYEA
(SEQ ID NO:7),

wherein A represents alanine, K represents lysine, Y
represents tyrosine, and E represents glutamic acid.

164. (Previously presented) The process of claim 155,
wherein the plurality of molecular weight markers is

AKKYAKKEKAACKAYKKEAKAKAAEAAAKEAAEYEA (SEQ ID NO:1);
AKKYAKKAKAEKAKKAYKAAEAKKAAKYEKAAAEKAAAKEAAEYEA (SEQ ID
NO:2);
AKKYAKKEKAYAKKAEKAAKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAEYEA
A (SEQ ID NO:3);
AKKYAKKEKAYAKKAEKAAKAEAKKAEAKKYAKAAKAEKKEYAAAEAKYKAEAA
KAAAKEAAEYEA (SEQ ID NO:4);
AKKYAKKEKAYAKKAEKAAKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAAAKEAAEYEA (SEQ ID NO:5);
AKKYAKKEKAYAKKAEKAAKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYA
AAEAKYKAEAAKAYKAEAAKAAAKEAAEYEA (SEQ ID NO:6); and
AKKYAKKAEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAK
AKKEAYKAEAKKYAKAAKAEKKEYAAAEAKKAEAAKAYKAEAAKAAAKEAAEYEA
(SEQ ID NO:7),

wherein A represents alanine, K represents lysine, Y
represents tyrosine, and E represents glutamic acid.